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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,141	02/06/2006	Ying-Duo Gao	21348P	2925
210	7590	01/14/2009	EXAMINER	
MERCK AND CO., INC			STOCKTON, LAURA LYNNE	
P O BOX 2000				
RAHWAY, NJ 07065-0907			ART UNIT	PAPER NUMBER
			1626	
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			01/14/2009	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/567,141	GAO ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Laura L. Stockton	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 05 November 2008.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-21 is/are pending in the application.  
 4a) Of the above claim(s) 16-21 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1-15 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
     1. Certified copies of the priority documents have been received.  
     2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
     3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____ .                                    |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>May 22, 2006</u> .  | 6) <input type="checkbox"/> Other: _____ .                        |

**DETAILED ACTION**

**Claims 1-21 are pending in the application.**

***Election/Restrictions***

Applicant's election of Group I in the reply filed on November 5, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 16-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no

allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 5, 2008.

***Oath/Declaration***

The Declaration fails to comply with 37 CFR 1.497(a)(2) since PCT/US2004/025036 is not identified in the Declaration. Applicant is required to submit a substitute declaration or oath to correct the deficiencies set forth in this communication.

***Information Disclosure Statement***

The Examiner has considered the Information Disclosure Statement filed on May 22, 2006.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutically acceptable salt of a compound of formula (I), does not reasonably provide enablement for a solvate of a compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in making an enablement rejection are summarized as:

- a) the quantity of experimentation necessary,
- b) the amount of direction or guidance presented,
- c) the presence or absence of working examples,

- d) the nature of the invention,
- e) the state of the prior art,
- f) the relative skill of those in the art,
- g) the predictability or unpredictability of the art, and
- h) the breadth of the claims.

In re Colianni, 195 USPQ 150 (CCPA 1977). In re Rainer, et al., 146 USPQ 218 (CCPA 1965). Ex parte Formal, 230 USPQ 546 (BPAI 1986).

- a) Determining if a particular compound would form a solvate would require synthesis and recrystallization of the compound solvate using a variety of solvents, temperatures and humidities. The experimentation for solvates is potentially open-ended.
- b) The specification merely mentions the Applicant's intention to make solvates, without teaching the preparation thereof.
- c) While the claims recite solvates, no working examples show their formation. As stated in Morton

International Inc. v. Cardinal Chemical Co., 28 USPQ2d

1190, 1194 (Fed.Cir. 1993) :

The specification purports to teach, with over fifty examples, the preparation of the claimed compounds ... However ... there is no evidence that such compounds exist ... [T]he examples ... do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The specification shows no evidence of the formation and actual existence of solvates. Hence, Applicant must show formation of solvates or limit the claims accordingly.

d) The nature of the invention is chemical synthesis of solvates, which involves chemical reactions.

e) The state of the art recognizes that the formation, composition and therapeutic activity of solvates is unpredictable. The Federal Circuit has recognized a solvate as an example of a polymorph or pseudopolymorph (emphasis added) :

"Polymorphs" are distinct crystalline structures containing the same molecules. These structural differences can affect various properties of the crystals, such as melting points and hardness (e.g., graphite and diamonds are both crystalline forms of carbon) .... [P]seudopolymorphs are often loosely called polymorphs ... Pseudopolymorphs not only have their molecules arranged differently but also have a slightly different molecular composition. A common type of pseudopolymorph is a solvate, which is a crystal in which the molecules defining the crystal structure "trap" molecules of a solvent. The crystal molecules and the solvent molecules then bond to form an altered crystalline structure.

SmithKline Beecham Corp. v. Apotex Corp., 74 USPQ2d 1398, 1409 (Fed.Cir. 2005). The same rationale obtains for hydrates; solvates in which the solvent is water. Souillac, et al., Characterization of Delivery Systems, Differential Scanning Calorimetry, pages 217-218 (in Encyclopedia of Controlled Drug Delivery, 1999, John Wiley & Sons, pages 212-227), recognize that different polymorphs of the same drug can have different therapeutic activity (emphasis added):

Because different polymorphic forms of the same drug exhibit significant differences in their physical characteristics, therapeutic activity

from one form to another may be different.  
Studying the polymorphism of a drug and the relative stability of the different polymorphs is a critical part of pre-formulation development.

Further, Vippagunta et al. (*Advanced Drug Delivery Reviews*, 48 (2001), pages 3-26) state "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult." See page 18, section 3.4.

f) The artisan using Applicant's disclosure to prepare the claimed solvates would be, e.g., an experienced process chemist with at least a BS chemistry degree.

g) Chemical reactions are known as unpredictable.

*In re Marzocchi, et al.*, 169 USPQ 367, 370 (CCPA 1971); *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). See above regarding the unpredictability of solvate formation.

h) The breadth of the claims includes thousands of compounds of the instant formula (1) as well as

presently unknown compounds embraced by the term solvates. See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicant's claimed invention.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United

States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 8 are rejected under 35 U.S.C. 102(a) as being anticipated by:

- a) the compound of CA Registry No. 515831-42-2 (indexed in the Registry file on STN May 15, 2003);
- b) the compound of CA Registry No. 515830-06-5 (indexed in the Registry file on STN May 15, 2003);
- c) the compound of CA Registry No. 515829-57-9 (indexed in the Registry file on STN May 15, 2003); or
- d) the compound of CA Registry No. 515120-36-2 (indexed in the Registry file on STN May 14, 2003).

Each of the above cited references disclose a compound that is embraced by the instant claimed invention. Therefore, each of the cited prior art anticipate the instant claimed invention.

Claims 1-6, 8 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by:

- a) Okada et al. {U.S. Pat. 4,950,668} - see, for example, Compound 158 in columns 39-40;
- b) Buzzi et al. {CA 67:98714, 1967} - see the compound of CA Registry No. 27739-75-9;
- c) Nakaya et al. {CA 79:42548, 1973} - see, for example, the compound of CA Registry No. 27739-72-6;
- d) Rubessa {GB 1209326} - see, for example, Example 3 on page 3; or
- e) Seltzman et al. {CA 137:370019, March 2002} - see the compound of CA Registry No. 475471-21-7.

Each of the above cited references disclose at least one compound embraced by the instant claimed invention. Therefore, each of the cited prior art anticipate the instant claimed invention.

Claims 1-6 and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Makriyannis et al. {WO 2003/020217}.

Makriyannis et al. disclose the compound of Int H on page 37, which is embraced by the instant claimed invention. Therefore, Makriyannis et al. anticipates the instant claimed invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-5, 10, 11 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okada et al.

{U.S. Pat. 4,950,668} and Rubessa {GB 1209326}, each taken alone.

***Determination of the scope and content of the prior art (MPEP §2141.01)***

Applicant claims pyrazole compounds. **Okada et al.** (see entire document; particularly columns 2, 3, 11 and 12 and the compounds in Table 2 starting on columns 39-40; and especially Compound 158 in columns 39-40) and **Rubessa** (see entire document; particularly 1, 3 and 8; and especially Example 3 on page 3) each teach pyrazole compounds that are either structurally the same as (see above 102 rejection) or structurally similar to the instant claimed compounds.

***Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)***

The difference between some of the compounds of the prior art and the compounds instantly claimed is that the instant claimed compounds are generically described in the prior art.

***Finding of prima facie obviousness--rational and motivation (MPEP***  
***S2142-2413)***

The indiscriminate selection of "some" among "many" is *prima facie* obvious, In re Lemin, 141 USPQ 814 (C.C.P.A. 1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g., digestive system regulators).

One skilled in the art would thus be motivated to prepare products embraced by the prior art to arrive at the instant claimed products with the expectation of obtaining additional beneficial products which would be useful as digestive system regulators. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is

(571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:00 am to 2:30 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

/Laura L. Stockton/  
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January 14, 2009